THESIS

for degree of

DOCTOR OF PHILOSOPHY

at

GLASGOW UNIVERSITY

by

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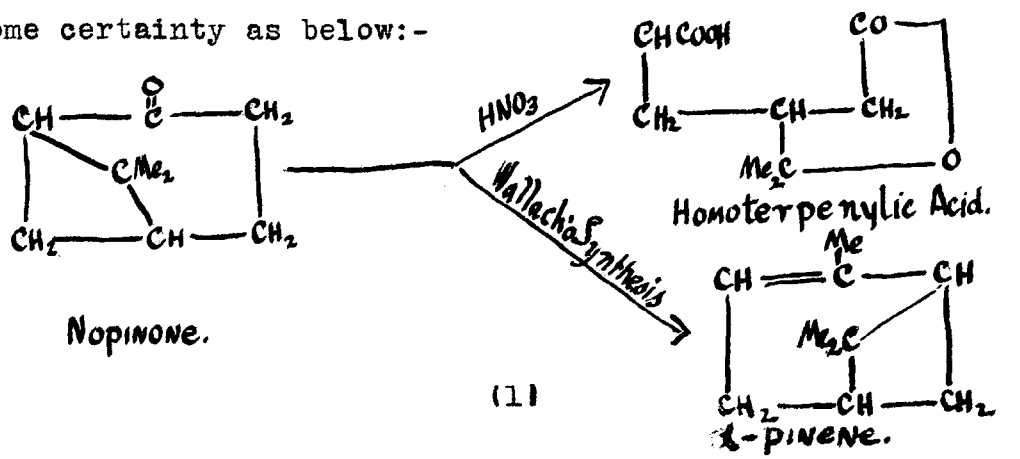
STUDIES IN THE TERPENES

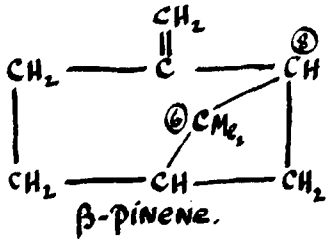
PART I.

ACTION OF HYPOCHLOROUS ACID ON β-PINENE.

Anattempt to prepare a chemically pure specimen of α-pinene from crude turpentine oil (Berthollet,Ann.de Chem. et de Phys. 39 p.5.) led to the isolation of a more or less pure form of the higher boiling fraction of that oil. Later on Wallach (Ann.Chem. 313.363.)whilst studying the oxidation products of French turpentine oil with $KMnO_4$, isolated nopinic acid, which he regarded as characteristic of the higher boiling fraction of that oil;and he called the terpene responsible for this acid nopinene. This terpene is now known as β-pinene,and is found to occur in all the varieties of turpentine oil,with the exception of the Alpine variety which is said to be a fairly pure d-α-pinene. Nopinic acid on oxidation gives nopinone,which is a very important substance since Wallach(Ann. 1908.363.1.) synthesised β-pinene from it.Nopinone is a cyclic ketone which gives homoterpenylic acid on oxidation; and it also gives α-pinene in the course of Wallach' β-pinene synthesis (loco.cit.).It can thus be represented with some certainty as below:-



These considerations prove that nopinone has the "pinene bridge", and hence β-pinene can be represented as follows:-



β-pinene.

The work done on β-pinene up to the present is briefly shown here

β-Pinene —HCl→ isobornyl chloride

.. —HBr→ isobornyl ~~chloride~~bromide

.. —NOCl→ no crystalline derivative

.. —O_2→ nopinic acid —O_2→ nopinone.

.. —3% H_2SO_4→ terpin hydrate.

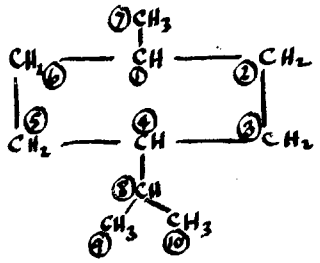
The only method yet available for the isolation of β-pinene is fractional distillation. Pariselle who has made a systematic investigation of the preparation and properties of pure α- and β-pinenes, calculated from optical measurements that French turpentine oil contains about 40% of β-pinene. According to him, two main factors govern the success of the separation of the two pinenes, viz., (a) a very slow rate of distillation, (b) an arrangement that the distillation flask is heated uniformly at 53m.m. using an Otto tube surrounded by an oil jacket kept at constant temperature, an fractionating column. Pariselle's physical properties for β-pinene are given here:

B.Pt. = 163°-164° C at 760 m.m.

N_d^{15} = 1.4790

d^{15} = 0.8728.

Recalling the action of the halogen acids on α- and β-pinene, it is well that in each case oneidentical products are got from the two isomers. Now Henderson and Marsh (J.C.S. 1921.1492-1500) have very satisfactorily cleared up the question of the action of hypochlorous acid on α-pinene, Wagner, Slawinski, and Ginsberg having previously worked on the same point with not such definite success These two workers found that hypochlorous acid on α-pinene produces menthane derivatives, the dimethylcyclobutane ring being severed between carbon atoms 6 and 5, using the ordinary numerical notation for the menthane molecule, as illustrated below:-



It should be interesting to know if the substituted tetramethylene ring in β-pinene also breaks down on treatment with hypochlorous acid or does the semicyclic ethlyene linkage inthis isomer stabelise the four membered ring; or again does intramolecular rearrangement take place and result in the same products as those from α-pinene and hypochlorous acid. It was with these points

in mind that the present work was taken up .

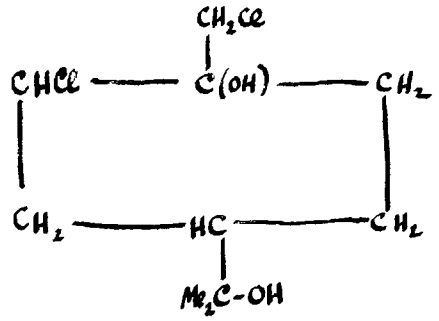
By a modification of Pariselle's method (loco cit.) both American and French turpentine oils were exhaustively frationated for β-pinene. As stated above Pariselle found that the rate of distillation and constant temperature bath were the most important factor in this separation. This view was confirmed in the present work, rapid distillation being found to be useless. The yield of β-pinene from the crude French oil was found to be about one per cent.

The pinene was treated with successive quantities of a very dilute solution of hypochlorous acid until saturation took place. From this treatment resulted a viscous oil, got by ether extraction of the aqueous part of the product, and a water insoluble oil. The former oil furnished on standing two crystalline products melting at 135°-136° C and 166° C, and later on another melting at 131°C. On analysis these were all found to be dichlorohydrins of the formula $C_{10}H_{18}O_2CL_2$ The one M.Pt.135° C. was decidedly the main product, the other two occurring in small quantities.

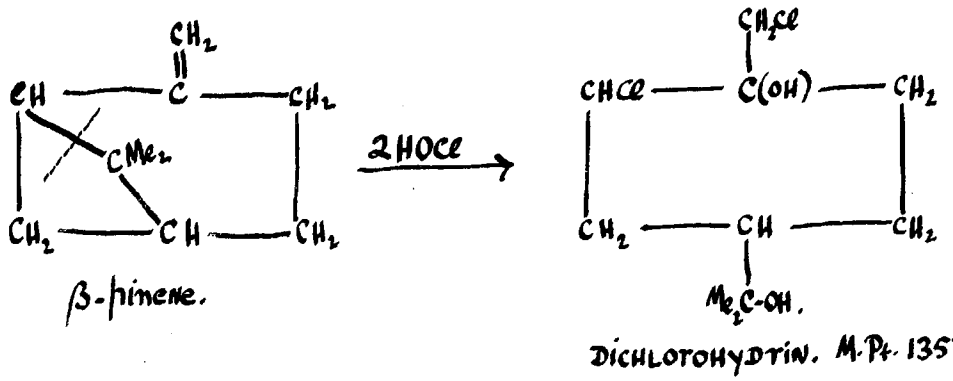
Dichlorohydrin M.Pt.135° C, is a white crystalline compound soluble in ether, methyl and ethyl alcohols, acetone and chloroform to a large extent, but rather insolyble in petroleum ether from which it can be crystallised. From a mixture of petroleum and dry ethyl ether it can best be crystallised in needles which take a star-like formation in groups. IT is optically active, having a

laevo rotation $[\alpha]_d^{15}$ = -75.0 in methyl alcohol solution. On treatment with p-nitrobenzoyl chloride in pyridine in the ordinway, it yields no nitrobenzoate, but it is readily attacked by dilute alkali to form amongst other things a monochlorohydrin of of the composition $C_{10}H_{17}O_2CL$.

Now Henderson and Marsh (T.C.S. 1921. 1492-1500), found one of the dichlorohydrins of d-pinene melted at 139°C, and identified it as sobrerol dichloride; but a mixed melting point determination proved that our dichlorohydrin, M.Pt. 135°C, was not sobrerol dichloride. From the fact that β-pinene adds on two molecules of hypochlorous acid, it is fairly certain that addition takes place at the double bond and between carbon atoms 6 and 8 (see formula for β-pinene in a previous page), the ring being severed in the process. The decomposition product, by the elimination of HCL by dilute alkali does not furnish any further clue to the structure of this dichlorohydrin, but remembering that only primary and secondary alcoholic groupings only react readily with p.nitrobenzoyl chloride one can reasonably suppose that two tertiary alcoholic groupings are present in this compound M.Pt. 135°C. The structure given below is the only one of the four possible position isomers having two tertiary alcoholic groups and represents best the known properties of the dichlorohydrin in question.



The formation of the above dichlorohydrin from β-pinene by the addition of two molecules of HOCL is indicated below:-



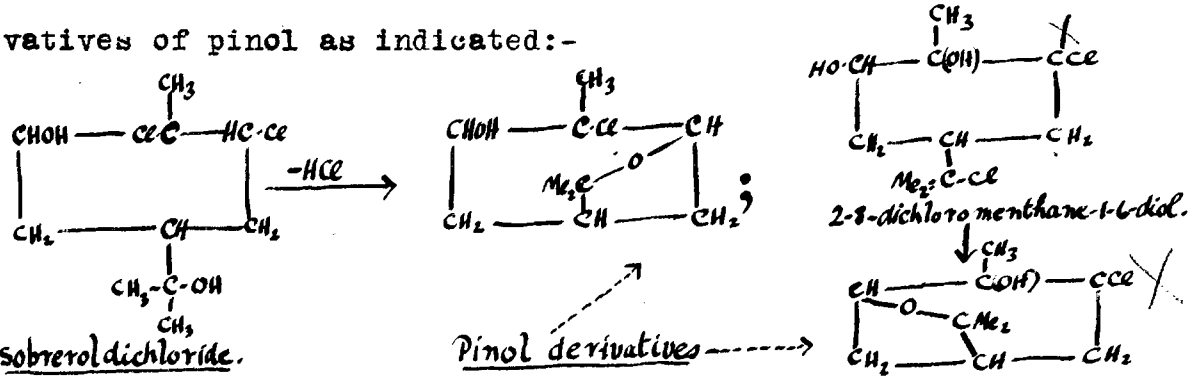
β-pinene.

DICHLOROHYDRIN. M.Pt. 135°C.

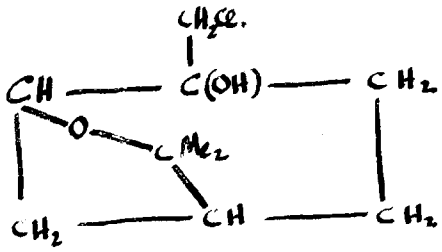
Dichlorohydrin M.Pt. 166°C, is not quite so soluble in ether, alcohol acetone as the former and is almost insolible in petroleum ether. It crystallises from a mixture of petroleum and ethyl ether in long silky fine needles. On treatment with dilute alkali the ether extract of the resulting solution furnished a non-crystalline oil, very soluble in all the common solvents. With dilu-te H_2SO_4 this oil does not produce an hydrated crystalline compound parallel with the action of dilute sulphuric on pinol oxide (Henderson and Marsh J.C.S. 1921.1492-1500). This oil is evidently not pinol oxide in spite of its similar smell. The smal quantity in hand prevented further investigation of the properties

of this oil.

One monochlorohydrin $C_{10}H_{17}O_2CL$, resulted from the dichlorohydrin M.Pt. 135°C. It crystallises in small prisms from petrol-eum ether and melts at 128°-129°C. A mixed melting point of this chlorohydrin with the optically active pinol glycol12-chlorohydrin showed that it was not identical with the latter—a conclusion which might have readily been arrived at in view of its method of formation and also of its melting point. Henderson and Marsh (lococit.) found that both sobrerol dichloride and 2-8-dichloromenthane-1-6-diol react with dilute alkali to give derivatives of pinol as indicated:-



From the above it can be deduced that the tendency of dihydroxy dichloromenthanes is to give the pinol bridge by the elimination of HCL.where this is at all possible. With this in mind,it is very reasonable to suppose that the chlorohydrin M.Pt 135°C, whose probable structure has been given above, on elimination of HCL willgive this compound here represented to correspond with the chlorohydrin in question:-



Monochlorhydrin.

There was a further crystalline substance got from dichloro hydrin M.Pt.135°C, by the action of dilute KOH solution. It forms well defined crystals of the cubic type and melts at 185°C It was formed from the mother liquor which furnished the monochlorohydrin $C_{10}H_{17}O_2CL$; and so this crystalline substance may be formed some monochlorohydrin by hydration at the pinol bridge. Hydration in this case would give a trihydroxychloromenthane, whose melting point should be in the region of 185-190° but it is questionable, on the other hand, if the pinol ring would be ruptured by dilute sulphuric at ordinary trmperatures.

To sum up the action of hypochlorous acid on β-pinene, it gives three dichlorohydrins distinct from those of α-pinene, and also a different monochlorohydrin from any of those derive from α-pinene; but it is seen that hypochlorous acid breaks the dimethylcyclobutane ring in each of the two isomers. TO this extent there is resemblance between the two isomers.

EXPERIMENTAL

ISOLATION OF β-PINENE.

The β-pinene used in this work was obtained, partly from American and partly from French turpentine oil. The commercial pil was allowed to stand over KOH sticks, to resinify aldehydes present, then steam distilled in the ordinary way, the last third of the steam distillate being collected for working up the xxxxx β-pinene. This method affords a partial separation of the two isomers present. Using a bulb fractionating column, the oil passing over from 160°-166° C was collected. On redistillation about 75% of this passed over about 160°C, and that part of the remainder distilling between 160°-166° C being collected. It was here found that the ~~higher~~ slower the rate of distillation the better the separation of the higher and lower boiling fractions. This fractionation was repeated over and over again, till ultimately a very small amount of β-pinene passing over constantly at 163°-165° C was obtained. By a long continuation of this process about ~~130~~ c.c. of pinene were isolated, having the following physical properties:-

B.Pt. at atmos. pressure	=	163°-165° C.
density	=	0.8710
N_d^{18}	=	1.4774

According to Pariselle the constants for pure α and β-pinenes are:

N_d for α-pinene = 1.4690

N_d for β-pinene = 1.4790

so that the following equation gives the percentage of pure pinene in the specimen in hand:-

$$x(1.4790) - (1-x)(1.4690) = 1.4774.$$

$$\text{or} \quad 0.01x = 0.9984.$$

$$x = 0.84.$$

"x" being the fraction of pure pinene in one part of the specimen. This shows only an 84% purity for the β-pinene even after exhaustive fractional distillation.

PREPARATION OF CRUDE DICHLOROHYDRIN PRODUCT.

About 120 c.c. of β-pinene were transferred to a large bottle and shaken up with a 1% solution of HOCL, prepared by Taylor's method (T.1912.101.). Absorption took place rapidly and a milky layer separated out below. This was syphoned off, saturated with salt and extracted with ether. On long continuation of this treatment a stage was reached when HOCL was no longer absorbed and a layer of water insoluble oil remained.

The ethereal solutions, got as above, were concentrated, dried an distilled, leaving a golden yellow oil soluble in all the common solvents. It was thoroughly dried by keeping it in a vcuumdessicator for some days. It was then allowed to stand in an ice-chest for

some considerable time, when a crystalline product separated out which was collected and partially purified from adhering oil by the filter pump. Four or five subsequent crops of crystals were were furnished by the oil, though the quantities decreasd each time To get rid of the last traces of the mother oil from these crystals a series of recrystallisations ~~were~~ was necessary from a mixture of petroleum and ordinary ether.

SEPARATION OF THE DICHLOROHYDRINS.

At this stage a melting point determination of the crude product indicated that a mixture of two or more subatances was present A tedious fractional crysrallisation from a mixture of petroleum and methylated ethers, led to the separation of two definite compon-ents melting at 135°-136° C, and 166° C, the latter one being the less soluble.

DICHLOROHYDRIN M.PT. 135°-136° C.

The substance M.Pt. 135° C, by a Carius estimation, shows a chlorine content of 29.04% as compared with the theoretical 29.46% for the formula $C_{10}H_{18}O_2CL_2$. It is a dichlorohydrin therefore and has $[\alpha]_d^{15} = -75.0$. About 0.3gm. of this dichlorohydrin was dissolved in 0.75gm. of pyridine, p-nitrobenzylchloride added slowly and heated intermittently for several days on a water bath. Excess of a very dilute H_2SO_4 was added till the pyridine smell disappeared and the solution filtered, leaving a yellowish solid on the filter paper which was washed with dilute Na_2CO_3 solution. This procedure got rid of P-nitrobenzylchloride or acid present.

The remaining solid was recrystallised from methyl alcohol. A melting point determination gave the melting point as 117°-120° C. Another recrystallisation revealed the fact that the substance was was unchanged dichlorohydrin, with a trace of p-nitrobenzoic acid present. This was suspected from the crystalline form of the product and verified by purification when the melting point registered 135°-136° C.

PREPARATION OF MONOCHLOROHYDRIN.

About 3gm of the dichlorohydrin mentiond above were treated with one molecular equivalent of KOH(0.5% solution) and mechanically stirred tillall the KOH was neutralised. Nearly all the dichlorohydrin was dissolved, though a little remained undissolved as was proved by its melting point when isolated and recrystallised. The resulting solution, after the KOH treatment was saturated with salt and extracted with ether, and on evaporation of the solvent a yellow oil was found. the oil was thoroughly dried and left to stand over a week, dissolved in a little petroleum ether in which it is not very soluble. No crystalline substance separated, and having got rid of the rid of the petroleum ether, the oil was treated with dilute H_2SO_4 (2% solution) in the hope of forming a crystalline hydrated product analogous to the formation of pinol glycol from pinl oxide. This procedure led to the separation of a cubic crystalline substance which on purification gave a melting point of 176°-178° C, and on successive recrystallisations ultimately melted at 185°-186° C. The ether

extract
solution of the acid solution was dried and the ether removed, leaving a viscous oil which crystallised to a white substance M.Pt. 128°-129° C . A Carius estimation for the chlorine cintent of this substance gave,

CL = 17.8%; calculated value for $C_{10}H_{17}O_2CL$ is CL = 17.3%.

This compound is therefore a monochlorohydrin. Amixed melting point of the monochlorohydrin with laevo-pinol-glycoll-2-chlorohydrin, of melting point 131°C. was found to be 110°C, a fact which proves that the two substances are not identical.

ACTION OF KOH ON THE MONOCHLOROHYDRIN.

The action of one molecular equivalent of dilute KOH(0.5%)solution, using the same methed as in the case of the dichlorohydrin above furnished asmall quantity of an oil which was in too small quantity for further investigation, attempts at crystallisation from many solvents having failed.

DICHLOROHYDRIN M.PT. 166° C.

Of the dichlorohydrin M.Pt. 166°C only approximately 2gm. could be isolated in the work. An estimation of the chlorine content gave ,

CL(found) = 29.62%; calculated for $C_{10}H_{18}O_2CL_2$, CL= 29.46%.

About 1gm. was treated with one molecular equivalent of dilute KOH (0.5%) solution and stirred till all the dichlorohydrin went into solution. The solution was neutralised with CO_2, saturated with salt extracted with ether and the ether solution dried over anhydrous

Na_2SO_4. On boiling off the ether, a yellow oil remained which could not be crystallised. The oil was treated with excess aqueous 2% sulphuric acid, left over for some time, then neutralised with $NaHCO_3$ and extracted with ether. The ether solution furnished no crystalline compound as was the case with dichlorohydrin M.Pt. 135° C. Using 0.15 gm dichlorohydrin an attempt was made to form a p-nitrobenzoate in the ordinary way, but no nitrobenzoate resulted.

PREPARATION OF DICHLOROHYDRIN M.PT. 130°-131° C.

The preparation of a third dichlorohydrin came about in this way For the purpose of preparing more of the monochlorohydrin mentioned in a previous page, the mother liquor, which furnished the two di chlorohydrins originally, was assumed to be of the composition $C_{10}H_{16}.2HOCl$ and was treated with dilute alkali and allowed to stand. The solution was neutralised with CO_2, saturated with salt and extracted with ether. On boiling off the ether a non-crystallisable oil resulted which was distilled in steam in the hope of isolating some mono-chlorohydrin in this way. The steam volatile oil, however, from this procedure furnished crystalls of a new substance which was found to contain 29.20% chlorine The theoretical for $C_{10}H_{18}O_2Cl_2$ is 29.46% of chlorine, so that the new crystalline compound is a new dichlorohydrin which melts at 130°-131° C. By a mixed melting point it was proved that this compound was not identical with sobrerol dichloride of M.Pt. 139° C, or with our dichlorohydrin, M.Pt. 135 C. Looking at the method of preparation of this dichloro

hydrin it may be reasonably assumed that it is stable towards dilute alkaline solution and dilute acid solution; and that, in fact, it would have resulted in a straightforward way by steam distillation of the original mother oil.

It may be mentioned here that the main difficulty of this work was the exceedingly small yield of product in all the reactions.

PART II

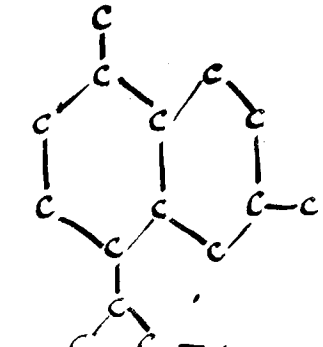
THE ACTION OF HYPOCHLOROUS ACID ON

β-CARYOPHYLLENE.

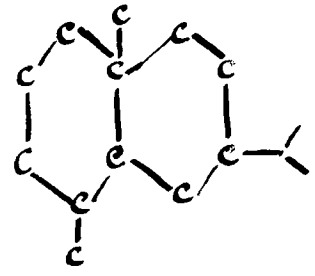
INTRODUCTION.

In addition to the terpenes $C_{10}H_{16}$, the higher boiling fractions of many volatile oils viz.- those between 250°-280° C, contain hydrocarbons corresponding to the formula $C_{15}H_{24}$ which have been named sesquiterpenes. These terpenes are classified as aliphatic monocyclic, dicyclic, tricyclic, the class being determined by the value of the molecular refraction and the density. The aliphatic sesquiterpenes, of which only one is at present known, viz. citronellene, contain four double bonds, the monocyclic three, the dicyclic two and the tricyclic one double bond. In general they are more viscid than the ordinary terpenes and have a more faint odour. Some give crystalline addition products with the halogen acids, NOCL, N_2O_3 and N_2O_4, which can be used for their identification. In the aliphatic, monocyclic and tricyclic sesquiterpene series nothing definite is known regarding the structure of the members therein, and the best known and largest variety occur in the dicyclic group, though even in this group nothing was known of their structure till in 1922 L. Ruzicka (HelvChem. Acta. A 1922 5. 345-368.) discovered that the carbon skelaton of many dicyclic sesquiterpenes were simply naphthalene skelatons with side

chains attached. He further discovered that many sesquiterpenes gave the same substituted naphthalenes on dehydrogenation with sulphur. HE has proved beyond doubt -and that by a synthesis of two of these substituted naphthalenes viz. cadalene and eudalene that many of the sesquiterpenes have either of the following skeletons;-



Cadalene Type.



Eudalene Type.

This discovery is a big step forward in the chemistry of the sesquiterpene field and marks the beginning of the end of the search for the constitution of many dicyclic sesquiterpenes. However outside the work mentioned here scarcely anything of a definite nature is known concerning the structure of the sesquiterpenes.

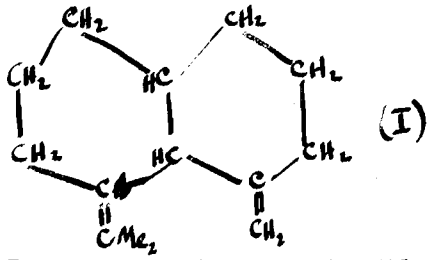
HISTORICAL.

Oil of cloves, copaiba balsam, cinnamom, lavender etc. contain a sesquiterpene fraction $b.p._{12}$ 132° ($C_{15}H_{24}$) which on further fractional distillation can be separated into two hydrocarbons, one laevo rotatory and the other inactive. The inactive one was identified as the sesquiterpene humulene (Deussen. J. f. Prakt. Chem. 1911.

which also occurs in oil of hops; and it is with the laevo isomer named by Deussen(Ann. 1908. 359. 246.) β-caryophyllene, that this work is concerned.

As early as 1893 (Wallach and Walker, (Ann. 271. 285-299) the sesquiterpene fraction from clove oil furnished a crystalline dihydrochloride, m.pt. 69°-70° C, which is now known to be β-caryophyllene dihydrochloride; and further by heating oil of cloves with glacial acetic and sulphuric acids, these chemists isolated an alcohol m.pt. 94°-96° C which is also a derivative of β-caryophyllene. The characterisation of β-caryophyllene, by means of its crystalline nitrosochloride, nitrosite and nitrosate, is due to Deussen(ANN 1907. 356. 1-23.: Ann. 1908. 359. 246.) and in 1914 he definitely showed that β-caryophyllene contained two double bonds, by forming crystalline addition products of the nitrosite, $C_{15}H_{24}N_2O_3$, with HCL and HBr(J.Prakt. Chem. 1914, 90(II), 318-335.). This was necessary when it is remembered that terpenes with only one double bond(pinene and sabinene) can give dihydrochlorides, and that also towards H_2 caryophyllene behaved as a substance with one double bond (c.f. J.f. Prakt. Chem 1914, 90(II). 318335.). Amongst the crystalline derivatives of β-caryophyllene, the nitrosite is the most interesting in so much as it has a distinct blue colour, and that on heating its alcoholisc solution it gives a new hydrocarbon(Deussen Ann 1908. 359. 246.). By reason of its blue colour it plays an important part in all structural formulae put forward for β-car

yophyllene, the blue colour indicating that the nitrosite has a "NO group attached to a tertiary carbon atom, and thus necessitating a doulbe bond adjacent to a tertiary cabon atom in the caryophyllene molecule. It may be mentioned that the following formula,

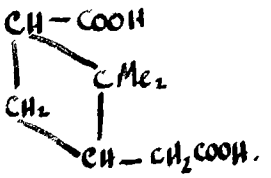


(I)

put forward by Deussen (Ann. 1909.369. 61-62.), was based on (a) the nitrosite evidence (b) on three products of oxidation by $KMnO_4$ concerning which nothing atall of the structure was elucidated. This formula has since been rejected as unsuitable, the author himself considering it untenable on account of the behaviour of β-caryophyllene on heating with sulphur (Deussen Zeit. angew. chem.1923 36. 348-349.) when it was he found no aromatic hydrocarbons in his product. Formula(I) should certainly lead to 1.5.dimethyl.4.isopropyl naphthalene on dehydrogenation by means of sulphur.

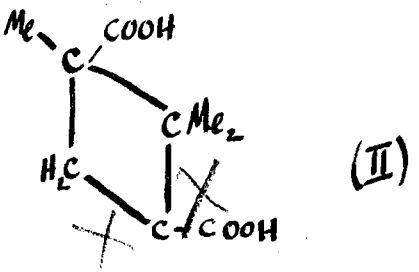
By acting on caryophyllene with O_3, a solid $C_{15}H_{24}O_6$ resulted (Semmler and Mayer, Ber. 1911.44. 3657-3679.) which broke down to give nine different products, of which two were CO_2 and HCHO. Of the remaining seven, five of these products gave on further oxidation succinic or dimethyl succinic accompanied by an acid $C_9H_{14}O_4$ named caryophyllenic acid. This acid is a liquid acid isomeric with the crystalline pinic acid obtained from α-pinonic acid and

which is well known to have the following structure:-



Pinic acid.

On account of its stability towards $KMnO_4$, HNO_3, its ability to give an anhydride and its high refractive index (n_d^{20} = 1.4462) Semmler (loco cit.) gives caryophyllenic acid the following structure:-

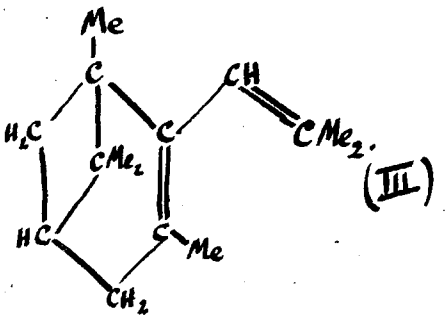


(II)

caryophyllenic acid.

or Cis-1.3.dicarboxy.2.2.3.trimethylcyclobutane.

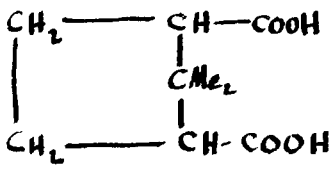
Based on his ozonide products, Semmler puts forward a formula for β-caryophyllene as follows:-



(III)

It is seen that Semmler based the above formula on his structure for caryophyllenic acid, and it would be well to examine his reasons for giving this acid a cyclobutane structure. On account of its high refractive index it is evidently of cyclic

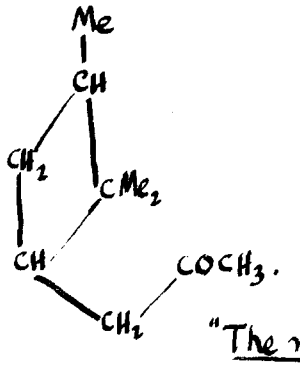
structure; and considering the formation of dimethyl succinic acid side by side with it in the further oxidation of the ozonide products, it contains a gem-dimethyl grouping. Since it is not identical with pinic acid and scince it cannot further have the cyclopentane structure indicated here,



Apo-camphoric Acid.

for this is apocamphoric acid, it is given the cyclobutane structure as written above. As will be seen although formula (II) is best suited to the known properties of caryophyllenic acid, this formula was addived at by an elimination process and cannot be strictly final.

Having fixed a structure for caryophyllenic acid, Semmler makes use of a ketone, $C_{10}H_{18}O$, -one of the ozonide decomposition products- to build up a further part of the molecule. This ketone acts with Br_2 in KOH to give CBr_4 and $C_9H_{16}O_2$ thus furnishing a proof that the ketone is of the type R-CO-CH_3. Now $C_{10}H_{18}O$ contains the caryophyllenic acid skeleton as it can loose two carbon atoms to give a cyclic monobasic acid $C_9H_{14}O_2$, thus it has a cyclobutane ring with a three membered side chain attached and is probably the following:-



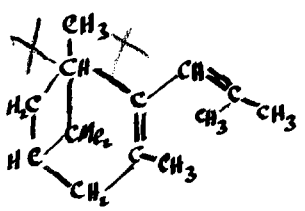
"The methyl ketone"

Thus far ten carbon atoms of the molecule have been accounted for and five still remain ,with two double bonds to be placed. From Semmler's oxidation by ozone which have any bearing on the further building up of the molecule,viz. a diketone $C_{12}H_{20}O_2$, a diketoaldehyde $C_{14}H_{22}O_3$,and a diketoacud $C_{14}H_{22}O_4$,it is extremely difficult to elucidate any useful infirmation as these substances are high boiling oils with no definite boiling point and are not securely characterised,e.g. $C_{14}H_{22}O_4$ was put down as a diketoacid because its semicarbazone had no fixed melting point and was judged to br a mixture of semicarbazones. Nor did the further oxidation of these products further the question in any way as they furnish only dimethyl succinic and caryophyllenic acids. However Semmler puts forward formula III* as the most probable structure for β-caryophyllene.

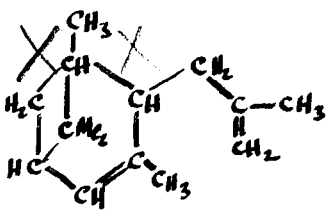
The matter is not finished at this on account of the further fact β-caryophyllene nitrosite on heating its alcoholic solution can give a new hydrocarbon,γ-caryophyllene.with physical properties quite distinst ,but lying quite close to those of β-caryophyllene. This γ-caryophyllene furnishes about 73% yield of the dihydrochloride of β-caryophyllene. Semmler then says that

page 21.

usual β-caryophyllene is a mixture of two isomers, which give the same dihydrochloride, and one of which furnishes the blue nitrosite. Though the literature of the subject is much confused at this point it seems to be tacitly assumed that the isomer which which gives the blue nitrosite is identical with the new hydrocarbon or γ-caryophyllene. Semmler represents caryophyllene by the two formulae below, the names "terp." and "lim." denoting that similar relationship as is found between terpinolene and limonene in the $C_{10}H_{16}$ series.



Terp. caryophyllene.



Lim. caryophyllene.

In the above reasoning for the presence of two isomers in β-caryophyllene Semmler overlooks the possibility that the blue nitrosite is a derivative of a single hydrocarbon- βcaryophyllene - and that it is capable of breaking down in such a way as to give a different hydrocarbon from that from which it was formed. This interpretation of the nitrosite evidence means that β-caryophyllene is not a mixture of two isomers; and it is in acc-ord withlarge yields of both the dihydrochloride and alcohol which were found to result from β-caryophyllene during the course of the present investigation.

It is seen therefore that Semmler's formulae are by no

means proven facts, and certainly beyond the arrangements of the first ten carbon atoms, do not rest on secure ground.

Up to the present the chief work done on β-caryophyllene is outlined here:-

(1) b.pt. 118°-119° C at 9.7 mm.; N_d^{15} = 1.5002.;

d^{15} = 0.9017.

(2) $C_{15}H_{24}$ —gl. acetic and sulphuric acids→ $C_{15}H_{26}O$ m.pt. 94°-96° C, caryophyllene alcohol.

$C_{15}H_{26}O$ —H_2O→ a tricyclic hydrocarbon, called clovene. $C_{15}H_{24}$

(3)

$C_{15}H_{24}$ —HCL in ether→ $C_{15}H_{24}2HCL$

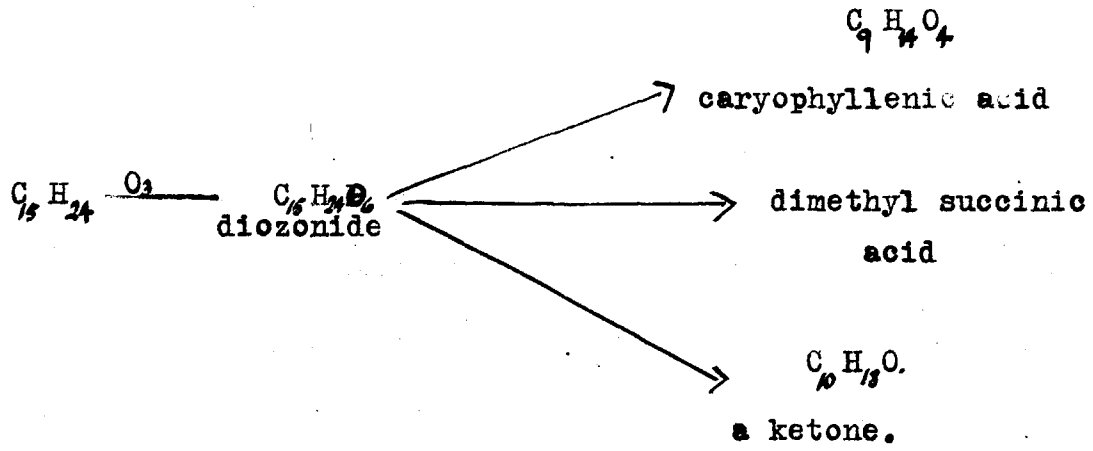
$C_{15}H_{24}2HCL$ —Quinoline→ a tricyclic hydrocarbon $C_{15}H_{24}$

$C_{15}H_{24}2HCL$ —KOH in CH_3OH→ a dicyclic hydrocarbon. $C_{15}H_{24}$.

(4) $C_{15}H_{24}$ —hydrogen→ a di- and tetrahydro derivative.

$C_{15}H_{26}$ and $C_{15}H_{28}$.

(5)



(6)

$C_{15}H_{24} \xrightarrow{N_2O_3} C_{15}H_{24}N_2O_3 \xrightarrow[\text{alcohol}]{\text{heat in}} C_{15}H_{24}$ or γ-caryophyllene.

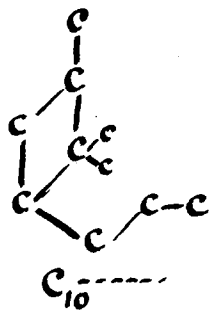
(7)

$C_{15}H_{24} \xrightarrow[200^\circ C]{S \text{ at}}$ no naphthalene or benzenoid hydrocarbons could be identified on the product.

Amongst the few conclusions of a general nature that can be made from the foregoing work, apart from those made by Semmler and mentioned above, are that β-caryophyllene is bicyclic (cf. (1)) has not a naphthalene skeleton (cf. (7)), and has a side chain which can accomodate itself to ring closure (cf. (2) and (3)). Much new experimental work is required to furnish more data before a satisfactory formula can be put forward for β-caryophyllene.

What is most required in the chemistry of β-caryophyllene is a series of oxidation products with all or most of the carbon skel-

eton of the molecule still intact. This would permit of a study of the membeRs of this series and also of their relation to the lower oxidation products isolated by Semmler (loco cit.). Some products of this type have actually been isolated (Haarmann, Ber. 1909, 42. 1062-1067; Deussen, Ber. 1909, 42. 376-381.), but nothing more of importance was done in that connection by these chemists than analysis of these products. Already, as has been seen, there is strong evidence for the existence, in the β-caryophyllene molecule, of a cyclobutane ring, having a gem-dimethyl grouping, and with a three carbon side chain to give the following skeleton:-

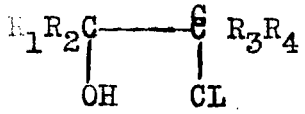


It is obvious that a study of oxidation products or their derivatives lying in the C_{10}-C_{15} region will furnish a clue as to the co-ordination of the remaining parts of the molecule; and such considerations prompted the present work.

THEORETICAL.

As β-caryophyllene, like many other terpenes, is very sensitive to oxidising agents, the oxidation proceeding direct to succinic or dimethyl succinic acids (cf. small yield of $C_4H_{22}O_4$ obtained by Deussen, Ann. 1903. 359. 258.), it was thought that HOCL might prove

a suitable reagent for this sesquiterpene. HOCL adds on to double bonds to give compounds of the following type,



called chlorohydrins, and which on treatment with dilute alkali pass over to the corresponding ethylene oxides. These latter (Henderson and Marsh T. 1921. 1492-1500; Henderson and Kerr T. 1924, 100-106.; Slawinski, Ber. 1899. 32 2064.) very readily pass over to the corresponding dihydroxy compounds on treatment with a 2% aqueous H_2SO_4 solution. This procedure in the case of β-caryophyllene, should furnish oxygenated derivatives with the fifteen carbon atoms still intact, and this plan was adopted.

This decision led to the necessity of preparing β-caryophyllene and HOCL, and a short account of these preparations is here given. As was indicated above, commercial caryophyllene contains two isomers, one optically active and the other inactive and of higher boiling point. No chemical separation of these two isomers is known up to the present and Deussen (Ann. 1907. 251. 1; 1908. 359. 245; 1909. 369 41.) to whom our knowledge of the presence of these two isomers is due, used fractionaldistillation at reduced pressure as a means of separation. Although caryophyllene can be distilled at ordinary pressures in the region of 260°C, it was considered that continued fractionation of the oil at this high temprature was apt to

bring about internal changes in the structure of the molecule and consequently it was decided to distill at reduced pressures.

The caryophyllene was obtained from Bush & Co. A preliminary investigation, by distillation at a pressure of 10 mm., showed that the oil was rich in β-caryophyllene, and on continued fractional distillation a lower fraction was isolated with the following physical properties:

B.pt. 118°-119° C/9.7 mm.; N_d^{17} = 1.5009; d^{17} = 0.9052.

This fraction did not permit of any further purification and was taken as relatively pure β-caryophyllene. As a further means of judging the purity of this fraction, the dihydrochloride was prepared and the result was an almost quantative yield of the crude crystalline dihydrochloride and about 75% yield of the pure salt m.pt. 68°-69° C. At this stage an attempt was made to crystallise some dihydrochloride of α-caryophyllene by freezing in CO_2 snow but failed and this supports the view that α-caryophyllene gives a liquid hydrochloride. It may be mentioned that the isolation of β-caryophyllene is a difficult and tedious operation and the chief difficulties were to keep the pressure constant and to prevent overheating of the oil. The second of these points is best attended to by keeping the Claisen surrounded by an oil bath maintained at that temperature which just allows the distillate to come over in drops at the rate of about one

per second; whilst at pressures ranging from 1.0 to 0.5mm. an almost constant pressure can be got by introducing into the reduced pressure system a large jar of about five gallons capacity.

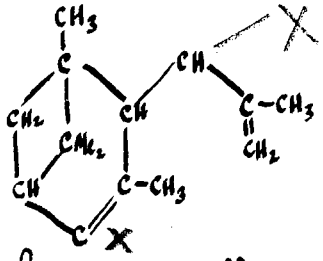
As a source of HOCL, Wagner and Slawinski (Ber. 1899. 32.2064) whilst Henderson and his co-workers (T 1921. 1492-1500; T 1923, 1156-1161; T. 1924. 101-106.) used a very dilute solution of aqueous HOCL obtained from bleaching powder and boric acid by Taylor method (T. 1913.101.44) Just recently however André Detoeuf (Bull de la Soc. Chim.1922. 102and 176.)has found an excellent way of preparing chlorohydrins by his being able to prepare monochlorurea $NH_2CONHCL$. This substanse in acid solution hydrolyses with the formation of HOCL and the regeneration of urea.

$$NH_2CONHCL + H_2O = NH_2CONH_2 + HOCL.$$

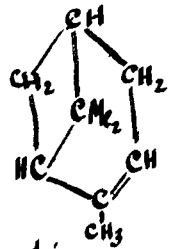
Monochlorurea is considerably stable and does not give off mush chlorine thus obviating the formation of dichloro- derivatives which occur to a greater or less extent when other sources of HOCL are employed; and moreover a concentration of monochlorurea in solution can be obtained by this method which is equivalent to a 30% HOCLsolution.

β-caryophyllene was treated with two molecular equivalents of monochlorurea in aqueous solution and the product separated from the aqueous solution, was a quantitative yield of a thick

brown oil which failed to crystallise from the common solvents or alone. A very small part was steam volatile, but this was found to be a mixture of dichlor-caryophillene and β-caryophyllene The residue after steam distillation was an unworkable resin, and could not be distilled at 10mm. without violent decomposition, resembling the original product from which it was derived in this respect. It may be here brought to notice that in one of Semmlers formula for caryophyllene viz.,



Lim.-caryophyllene.



α-pinene.

there exists the same system as is found in α-pinene, i.e. a cyclobutane ring conjugated with a double bond, and as G. Dupont (Bull. Soc. Chim. 1922 (iv). 897-909) points out, a system of this kind can, not only act as a substance with one unsaturated bond, but also can take up two molecules of the halogen acids, HOCL and H_2O. That in all probability the cyclobutane ring of α-pinene did occur in β-caryophyllene was seen in a previous page, and apart from adopting the above formula on detail, it was reasonable to suspect β-caryophyllene of being able to unite with three molecules of HOCL. The suspicion was neither proved or disproved since the product from treating $C_{15}H_{24}$ with 3HOCL molecules was even less amenable to steam distillation, crystallisation, or

low pressure distillation. It was evident by this procedure that a very complex reaction was taking place and it was decided to reduce the velocity of reaction by cooling and also to give the reacting substances a more intimate mixing by using acetone as solvent for β-caryophyllene, with about 10% of water present. Accidently also acetone was seviceable in that the rate of hydrolysis of NH_2CO HHCL, and consequently the rate of addition of HOCL, was greatly diminished in this solvent. The procedure in this treatment was briefly to dilute the hydrocarbon with five times its volume of acetone and slowly add the monochlrourea whilst cooling at the water tap. This procedure furnished a good yield of a bright yellow oil which failed to crystallise from solvents or alone. At this stge it was not free from chloroacetone, formed during the course of the reaction, and the product, being unsaturated towards Br_2 and $KMnO_4$, was suspected of containing free $C_{15}H_{24}$ or $C_{15}H_{24}CL_2$ or both. AT 10mm. pressure an attempted distillation of a sample of the oil resulted in much decomposition, and it was necessary to employ a McLeod guage, a mercury pump, amd the water pump to obtain a pressure of 1 mm. at which prssure a satisfactory distillation of the crude chloro-product was obtained. The scheme of fractionation in this case was based on the fact that the chlorohydrins sought should be saturated towards Br_2 and $KMnO_4$ together and the scheme was put onto operation by dividing the

distillates into five parts and testing the unsaturation of these by Br_2 and $KMnO_4$. The higher boiling fractions furnished ultimately a fraction 125°-140° at 1m.m., fully saturated towards Br_2 and $KMnO_4$ and boiled almost constantly between the two described temperatures. This fraction on two consecutive analysis was proved to have the formula $C_{15}H_{24}O\ CL_2$ and its physical properties are given here:

B.Pt 125°-140° C at 1mm; $N_d^{16} = 1.5019$.

$\alpha_{Hg\ blue}^{16} = -3.70$ in 5.17cm. tube in 30% C_2H_5OH solution

The compound $C_{15}H_{24}O\ CL_2$ was treated with its molecular equivalent of p-nitrobenzoyl chloride in the usual manner in pyridine solution. The product isolated in the usual manner for a nitrobenzoate, was unsaturated, contained no nitrogen, and so proved that the "O" in the compound is not in the form of a primary or secondary alcoholic grouping, and further that the pyridine solution at the temperature of reaction eliminated some part of the chlorine from the molecule in the form of HCL

Semicarbazide acetate in alcoholic solution, on standing for a considerable time failed to crystallise give any crystalline semicarbazone and the product isolated by precipitation by water proved to be saturated, to contain no nitrogen, and presumably was unchanged $C_{15}H_{24}O\ CL_2$. It is not an aldehyde and so

the oxygen in this compound is not of the carbonyl type.

From these considerations and from the mode of formation of $C_{15}H_{24}O\ CL_2$, it is reasonable to suggest that it contains an inner oxide grouping, two "OH" groups of a hypothetical dichlorohydrin losing water either during distillation or spontaneously on formation of the supposed dichlorohydrin. That water was eliminated during distillation will be seen later on in the work. Now this oxide is of the 1-2, 1-3, 1-4, or 1-5 inner oxide type. Ethylene oxides of both straight chain and cyclic compounds(cf. Petoeuf, Bull de la Soc Chim. 1922.(4) 31 131-169-176; J.Von Braun and Schirmacher Ber. 1923. 56. 1845-1850.) are readily hydrated to the corresponding glycols either by boiling with water or by the action of a very dilute solution of aqueous H_2SO_4. The compound is quite stable towards cold aqueous 2% H_2SO_4; nor does any action take place on adding alcohol to promote more intimate mixing of the oxide and the aqueous alcohol, nor even on warming the latter. After this treatment the recovered product, with the same physical appearance as the starting substance, gave no sign of alcoholic groupings when tested by p-nitrobenzoyl chloride. The oxide does not behave as a 1-2 inner oxide or an ethylene oxide.

A solution solution of 0.5% KOH has no effect in the cold on the oxide, no KCL being eliminated. On heating however, a 0.5% KOH in dilute aqueous alcohol did eliminate some KCL, and it was thought that the action might have taken place as follows:-

$C_{15}H_{24}O\ CL_2 \xrightarrow{H_2O} C_{15}H_{24}CL_2(OH)_2 \xrightarrow{KOH} C_{15}H_{24}O_2 + HCL$ (or KCl+H

intermediate dichlorohydrin.

a di-(ethyleneoxide)

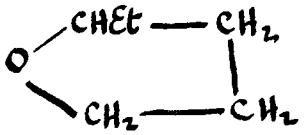
This unfortunately was not the course of the reaction, as the product, still containing traces of chlorine, behaved as an unsaturated substance and would not hydrate to the corresponding tetra-hydroxy compound on treatment with a 2% H_2SO_4 solution, as a di-(ethylene-oxide) should. Again α-β-halogen-hydroxy compounds, e.g. chlorohydrins, iodohydrins etc., have been found to give ketonic compounds on treatment with reagents that remove halogen acids. The intermediate inner oxide is said to isomerise as follows;-

$$R\underset{H}{\overset{OH}{C}}-\underset{X}{CH_2X} \xrightarrow{-HX} R\underset{O}{CH}-CH_2 \longrightarrow RCH_2-CHO$$

This isomerisation is known as the Tiffeneau rearrangement (cf. Michael, J.Amer. Chem. Soc. 192p. 42. 810; Tiffeneau, Bull. Soc Chem. 1907.(4).1205.). Although a study of the Tiffeneau rearrangement would not, in the case of removal of HCL from $C_{15}H_{24}O\ CL_2$ to give $C_{15}H_{24}O_2$ via an itermediate dichlorohydrin, give strong reason to suspect the presence of ketonic groupings in the product, it is well to note that the product from treatment from of $C_{15}H_{24}O\ CL_2$ with dilute alcoholic KOH does not give ketone or aldehyde reactions, and the product seems to be a mixture of dichloro-oxide ($C_{15}H_{24}O\ CL_2$) and a little of the latter with HCL removed.

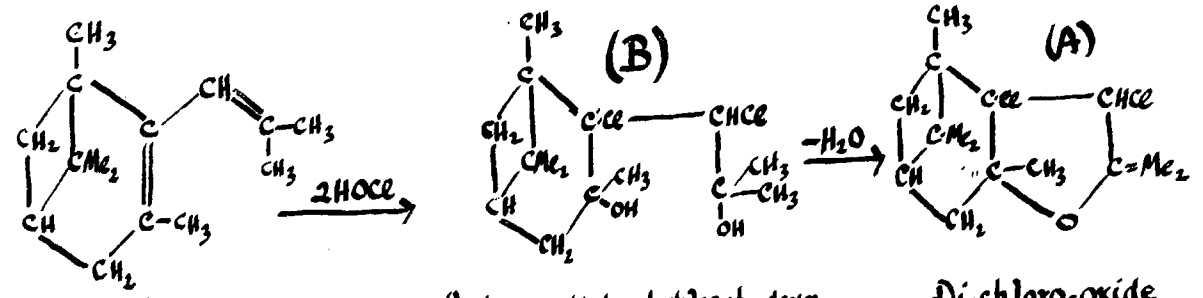
From a paper by A. Franke and F. Lieben (Monatsh. 1914. 35. 1431-1433.) who worked on the dehydration of glycols one would con-

clude that those glycols which furnish the most stable oxides are the 1-4 and the 1-5 variety, e.g. 1-4 hexylene oxide,



1-4-hexylene oxide.

was prepared by these chemists and found to be quite stable. It is also evident from this paper that 1-4 and 1-5 glycol structures most readily ~~gi~~change to the oxide grouping, as might be expected if Bayers strain be adopted here. Now from the stability of $C_{15}H_{24}OCl_2$ and from its formation during distillation by elimination of water it is reasonable to suppose that it may be a 1-4 or 1-5 inner oxide; and if Semmlers ter.caryophyllene formula be adopted for the moment a 1-4 inner oxide seems most suitable, as is seen from the following representation of the course of the reaction of HOCL on the hydrocarbon:-



β-Caryophyllene. $C_{15}H_{24}$

Intermediate dichlorohydrin. $C_{15}H_{24}(HOCl)_2$

Di-chloro-oxide. $C_{15}H_{24}OCl_2$

It might seem hypothetical to conclude that, before distillation

any dihydroxy compound had existed at all in the crude product, but to support the existence of such an ester of the type $C_{15}H_{25}O\ CL_2(OOCCH_3)$ was able to be isolated from this product. By the usual method a crude esterified product was isolated which on fractional distillation at 12mm. pressure, yielded a fraction b.pt 190°-200° C. This fraction having,

$N_D^{20} = 1.5213.$ $(\alpha)_{Hg\ blue}^{20} = -0.74$ in 5.17cm. thube in 10% alcoholic solution.

was a yellow oil with a composition,

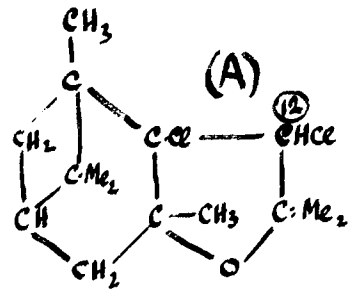
C = 57.11% H = 6.93% CL = 19.9%.

Considering the difficulty of purification of this ester, these figures agree reasonably well with,

C = 58.12% H = 7.97% CL = 20.22%

which are the calculated values for the formula $C_{15}H_{24}(OH)CL_2(OOCCH_3)$ and at any rate the figures found experimentally do not admit of any other satisfactory explanation. The existence of this monoacetate shows that a dichlorohydrin existed in the crude product. Attempts to prepare the p-nitrobenzoates of the crude product failed, perhaps due to the presence of mono-chloracetone and dichlorcaryophyllene, or perhaps due to the existence of the hydroxyl groups as tertiary alcoholic groupings.

Formula (A) again illustrated below although it must be treated as purely tentative, corresponds strikingly with the known properties of the oxide in questione.g. $C_{15}H_{24}O\ CL_2$.



(A)

$C_{15}H_{24}OCl_2$.

Its resistance to hydration agrees with the five membered heterocyclic structure; the tenacity ,also,with which it holds some ø of its chlorine is demonstrated by boiling with aniline for many hours when the product still contains chlorine,and this is in agreement with thefact that carbon atom (12) connot readily part with its chlorine owing to the absence of an adjacent hydrogen atom. Also a study of formula(B)* shows that both OH groups are tertiary which could account for the inability of the crude p product to react with p-nitrobenzoyl chloride.

With a view to obtaining a compound of the type $C_{15}H_{26}O$ from $C_{15}H_{24}OCl_2$ a portion of the oxide was treated with Cu-Zn dust in alcoholic solution containing some water. This process was extremely tedious,and after three weeks refluxihg of the ingredients the oxide still contained an appreciable quantity of chlorine and and attemts to perform a fractional distillation at reduced pressure on the partly dechlorinated product were unsuccessfull.Prolonged ~~boiling~~/ treatment with Na-amalgam in absolute alcohol,was not successful either, but a determination of the carbon,hydrogen and chlorine contents of the partly dechlorinated substance,showe

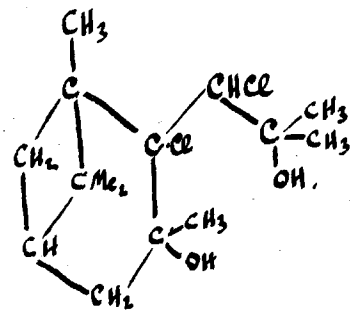
* Page 36.

showed that the dechlorination was taking place according to anticipation, and that roughly about 60% of the oxide was dechlorinated after a two weeks treatment. These dechlorinations were put down as failures due to their extremely slow action.

An attempt to oxidise $C_{15}H_{24}O\ CL_2$ by CrO_3 in glacial acetic acid, molecular quantities of each being used, showed that the oxide is quite stable towards $Cr\ O_3$ at ordinary temperatures. At the temperature of the water bath, however, oxidation proceeded and the product was solely a neutral oil b.pt. 140°-165° at 0.7mm, which on analysis could not be reconciled to any formula, and was considered a mixture unable to be separated by fractional distillation. The stability of $C_{15}H_{24}O\ CL_2$ towards cold CrO_3 is again in agreement with formula (A), and definitely establishes the absence of an alcoholic grouping in this compound. H_2O_2 in glacial acetic acid solution at the ordinary temperature oxidised $C_{15}H_{24}O\ CL_2$ to a neutral and two acidic products. Of the acidic products one, which occurs in small yield, was identified as succinic acid whilst the other and main product of the reaction was a brown oily acid of viscous appearance and now further characterised.

Although the first aim of this work was not completely realised i.e. preparation of an oxygenated derivative of caryophyllene containing the fifteen carbom atoms, this was due to the unforseen tendency of the starting compound to loose water on distillation in such a way that regeneration was impossible. There is definite evidence to support the existence of at least one dichlorohydrin of β-caryoph-

yliene and by a study of the oxide into which it passes readily, quite a number of facts were brought to light concerning its structure e.g. it cannot be distilled at reduced pressure without loss of water; it probably contains two tertiary hydroxyl groups; it is capable of giving a mono-acetate. On the total data furnished by a study of the oxide mentioned, the following formula for a dichlorohydrin of β-caryophyllene is suggested:-



Di-chlorohydrin of β-caryophyllene.

EXPERIMENTAL

Preparation of pure caryophyllene.

The source of the β-caryophyllene used in this work was an oil obtained from Bush& Co., guaranteed to contain caryophyllene sesquiterpenes and with no statement as to its physical properties. Metallic Na had no action on a sample of the oil dried over anhydrous Na_2SO_4, and only slight resinification took place on treatment with KOH sticks. A large quantity of the oil, having been dried over anhyd. Na_2SO_4 and treated with KOH, was stored in a large bottle for subsequent frational distillation. The physical properties of the oil thus treated were,

$$D\ d^{19} = 0.9076. \qquad N_a^{19} = 1.5021.$$

Using a Claisen flask of 250 c.c. volume, attached to a Brukl receiver and a water pump, a distillation was performed and showed that roughly 25% 75% boiled at 119-122 C at a perssure of 10 mm., the remainder boiling at 122-128 C. By a continuous distillation at a rate of one drop of distillate per second, with an oil bath kept at 170°-175° C, the lowest boiling oil was collected and found to have the following physical properties (the refractive index was read from an Abbe REfractometer):-

b.pt. 118°-119° at 9.7mm.; $N_d^{17} = 1.5009$;

$[\alpha]_D^{14} = -8.30$; $d^{19} = 0.9052$;

Preparation of β-caryophyllene dihydrochloride.

A sample of freshly distilled β-caryophyllene, b.pt. 118°-119° C at 9.7 mm., was dissolved in about three times its volume of ether which had been previously distilled twice over Na. HCL gas, dried by H_2SO_4 bubblers, was passed in while the containing flask was kept in an ice-salt freezing mixture. The resulting dark red liquid contained in solution the hydrochloride which was isolated by evapourating the ether by a current of dried air, taking care that no moisture entered the flak containing the hydrochloride, as this reduces the yield of crystalline product to a great extent. The dark mass ø of crystals were purified first by filtration at the suction pump and finally by recrystallisation from purified ethyl alcohol, which proved the best crystallising solvent. After several recrystallisations a m.pt. was found to be 68°-69° C as compared with Wallach and Walker's (A.E. 1893.101) melting point of 69°-70° C. BY collecting all the crystalline dihydrochloride possible, the mother liquors being repeatedly frozen for this purpose, a yield of 75% pure product was obtained.

A fraction 125°-127° C, which proved to be the highest boiling fraction in Bush's oil, was treated exactly as above with HCL, but the yield of crystalline product only amounted to about 10% the theoretical. An attempt to recrystallise the mother liquor of this latter, which liquor was undoubtedly α-caryophyllene dihydrochloride filled by freezing in CO_2 snow proved a failure. The dihydrochloride m.pt. 69°-70° C, was dissolved in ethyl alcohol to give a 2.5% solut-

ion,of which the optical rotation was determined and found to be strongly dextrorotatory as was also noticed by Semmler and Mayer (BER. 1910.43.3451.)

$(\alpha)_d^{15} = 0.84$, length of tube = 5 dem., concentration = 2.5%.

$$\therefore [\alpha]_d^{15} = 100 \times \frac{\cdot 84}{2 \cdot 5 \times 5} = 100 \times \frac{8 \times 84}{1000}$$

$$= +67 \cdot 2^{\circ}.$$

Preparation of monochlorurea.

To 12p gm. urea mixed with 60gm. roughly crushed marble rock ($CaCO_3$) in a large necked bottle witha two holed rubber stopper 60 gm of water were added. Having fitted the bottle with the necessary glass tubing,chlorine was bubbled through the semi solid mixture until the CL_2 was no longer absorbed noticeably by the urea. This end point can be guaged by noting a tendency to froth on the part of the contents of the bottle,or by successive weighings until the theoretical increase is attained..It required about 2to 2½ hours to complete this stage,and beyond this stage the further passageof CL_2 diminishes the yield of monochlorurea. It was ~~no~~ not necessary to separate monochlorurea in the crystal state.the contents of the bottle being simply separated by filtration from the unused marble. The solution of monochlorurea which measured about 150cc. was diluted to 300cc. and the amount of monochlorurea present was estimated by titration against standard thiosulphate, adding a little acetic acid to bring about the hydrolysis of the

monochlorurea. In a number of preparations ranging from of monochlorurea, a yield of the latter ranging from 108-126 gm. was obtained from a starting 120gm. of ureaM.

Preparation of crude chlorohydrin product.

From 120gm. urea, a solution of monochlorurea containing 108gm. was prepared as in the previous paragraph. This amount furnishes sufficient HOCL for 117cc. of caryophyllene calculated on the basis of two HOCL molecules for one caryophyllene molecule. So about 120c of β-caryophyllene b.pt. 118-119/9.7mm were diluted to about 600cc. with acetone in a large flat bottomed flask containing 10cc. of gl. acetic acid, and whilst being cooled and agitated beneath a water tap the required amount of monochlorurea was added slowly. If the Mmonochlorurea is added in large quantities it is difficult to maintain the contents of the flask at the temperature of tap water, and rise in temperature results in low yields, due in some measure to the formation of monochloracetone. To bring the reaction to completion, the contents of the flask were transferred to a stout Winchester bottle, tightly stoppered, and placed on a mechanical shaker for about six hours. In some cases more than six hours were required, the end point being judged by the action of a sample of the reaction mixture on an acidified KI solution, a very weak colouration denoting completion. At this stage the liquid, having assumed a two layer position on standing, was distilled from a water bathwhen most of the acetone solvent was recovered. The residue was extracted with ether to get rid of urea. Theether extracts were

concentrated, dried over anhyd. Na_2SO_4, and distilled on the water - bath, leaving in distillation flask the crude chlorohydrin product, which was not able to be crystallised by any method.

In two previous attempts to prepare chlorohydrins, one using two molecules of HOCL, other three molecules HOCL for every molecule of $C_{15}H_{24}$ (see theoretical part of this treatise, p.31) the preparation was similar to above one except that water was used instead of acetone which of course makes unecessary the first distillation mentioned in above preparation.

Action of p-nitrobenzoyl chloride on crude product.

A sample of the crude chloro-product was dissolved in ten times its weight of pyridine and a little more than the theoretical weight of P p-nitrobenzoyl chloride (assuming that crude product to be approximately $C_{15}H_{24}2HOCL$) to give a di-p-nitrobenzoate, was slowly added. The reaction mixture stood at water-bath temperature during about 45 hours, when, by the usual treatment for isolation of a nitrobenzoate a thick brown product resembling chewing gum resulted. This proved to be a machanical mixture of nitrobenzoic acid and a thick oily liquid which did not give the usual test for nitrogen but contained chlorine and was unsaturated toqards Br_2 in $CHCL_3$ solution. Evidently pyridine at the temperature of reaction has abstracted part of the chlorine as HCL from the molecule to give an unsaturated compound.

Preparation of ester of composition $C_{15}H_{24}CL_2OH.(OOCCH_3)$

About 15 gm. of the crude productwere dissolved in a slight excess

of acetic anhydrideover the calculated amount necessary to esterfg two hydroxyl groups in the molecule(assuming crude product to be $C_{15}H_{24}(HOCL)_2$). A small drop of conc. sulphuric was added and on warming a few minutes action took place,giving a brown yellow product. The product was poured into a solution of $NaHCO_3$,extracted with ether,and the dried ether extracts evapourated down on the water bath giving a brown syrup,which failed to crystallise from a large variety of solvents or alone. The brown syrup was found to distil at 12 mm.,boiling over a range of 40°C. From this by continued distillation,three frations were isolated of which the middle one only furnished any satisfactory figures on an ultimate analysis. This middle fraction on further purification by distillation boiled at 190°-200° C /12mm. and on analysis gave the following figures:-

C = 57.06%, H= 6.85% CL = 19.9%.
C = 57.11% H = 6.93% CL = 19.9%. } (experimantal)

Theoretical for $C_{15}H_{24}CL_2(OH).OOCCH_3$.

C = 58.12%, H = 7.07% CL = 20.2%

The physical properties found were,

B.Pt. 190°-200° C/12mm. : N_d^{20} = 1.5213. :

The yield of this ester was small and approximately 12% of the weight of the starting product.

Preparation of $C_{15}H_{24}O\ CL_2$.

The yellow oil which is described above as 'crude product'would not distil at 10mm pressure without considerable decomposition,and

for the purpose of obtaining a lower pressure a Hg-vacuum pump was fitted in series between a Bruhl receiving apparatus and a water/pump, all of which were in connection with a 100cc. Claisen flask containing the crude chlorohydrin product. It was found that Claisen flasks larger than 100cc. were not satisfactory, for the reason that in the larger flasks, the exhaust pumps were not able to cope with the gaseous decomposition fumes, which are always formed to a greater or less extent when on distillation of this compound. This of course makes the pressure rise and accordingly the necessary temperature for distillation is increased with a correspondingly greater amount of decomposition, and then another rise in pressure and so on till an equilibrium is established by the exhaust pumps. Also at low pressures like 1mm., it was found advantageously to seal up one limb of the Claisen, and keep a supply of fresh porous pot in the flask whilst distilling.

At a pressure of 1 mm., the following fractions were collected in the receiver,

(1) 70°--95° C

(2) 95°--110° C

(3) 110°-125° C

(4) 125°-145° C

(5) 145°-164° C.

(1) and (2) were unsaturated towards Br_2 and alkaline $KMnO_4$, and contained Cl. (3) is saturated towards $KMnO_4$ but unsaturated towards Br_2. (4) and (5) are saturated towards Br_2 and $KMnO_4$. The highest fraction of

(2) was added to (3) which on refractionation was added to furnished a higher fraction which was added to (4). On a continuous fractionation of this kind, a fraction b.pt. 125-140° C/1mm., saturated to both Br_2 and $KMnO_4$ was obtained. This fraction on analysis gave,

C = 62.36% : H = 7.89%: CL = 23.4% : } (experimental.)

C = 62.26% : H = 7.86% : CL = 23.40% : }

against theoretical for C H O CL ,

C = 61.8 % : H = 8.24% : CL = 24.0% : (calculated).

Physical properties of the fraction in question were,

B.Pt. 125-140 C/1mm. : N_d^{16} = 1.5019 : $(\alpha)_{Hg}^{16}$ = -3.7 in 5.0 cm. tube in 30% alcoholic solution.

Test for alcoholic grouping in $C_{15}H_{24}O\ CL_2$:

On treatment of a sample of $C_{15}H_{24}O\ CL_2$ in pyridine solution with p- nitrobenzoyl chloride in the usual way for several days, the product isolated by neutralisation of the pyridine by dilute H_2SO_4 at about 10° C, filtration ,and repeatedly washing the solid thus got by $NaHCO_3$ was a brownish oil, unsaturated to Br and, giving a test for CL by the usual method and giving no test for nitrogen.

Test for carbonly groupings in $C_{15}H_{24}O\ CL_2$.

Assuming $C_{15}H_{24}O\ CL_2$ to have one 'CO' group, a molecular equivalent of prepared semicarbazide acetate in alcoholic solution was added to a known weight of the compound. This stood about ten days at ordinary

temperature ,a few drops of water being added in the latter stages to aid crystallisation of any semicarbazide that might be formed. No crystalline compound separated and the product got by precipitation with water, was saturated and contained no nitrogen. $C_{15}H_{24}O\ CL_2$ shows no aldehydic properties when treated with ammonaical $AgNO_3$ solution.

Action of 2%H_2SO_4 on $C_{15}H_{24}O\ CL_2$:

A sample of $C_{15}H_{24}O\ CL_2$ was placed in a small bottle ,a large excess of aqueous 2% H_2SO_4 added, and the bottle tightly stoppered was shaken mechanically for two days. None of the oil went into solution, and on recovery the oil gave no p-nitrobenzoate, indicating that the 2% H_2SO_4 had no action on it. In a small conical flask,more was treated with 2% H_2SO_4 on the water bath for about twelve hours, without any of the oil going into solution. On adding a quantity of oil to this about 25% ofbthe oil went into solution and on refluxing this alcoholic solution for about 6 hours, the product isolated by distillin off the alcohol,and decanting the remaining aqueous solvent,was a brown yellow oil, similar to the original and gave no ester of p-nitrobenzoic acid.

Action of 0.5% KOH on $C_{15}H_{24}O\ CL_2$.

A quantityof $C_{15}H_{24}O\ CL_2$ was shaken up for several hours with twice an equivalent molecular quantity of 0.5% KOH solution. No trace of KCL could be detected in the aqueous layer after this treatment.With a little alcohol added to promote more intimate mixing of the oil and aqueous layer,shaking was continued for one day,but only a extremely

faint trace of KCl could be detected. With a little more alcohol added the reacting substances were kept in a flask at about 70°C for 5 days when mosy of the oily substance went into solution. On removing alcohol by distillation, a product was got containing a trace of CL and was unsaturated. To find if this product contained any 1-2 inner oxide compound, it was shaken for a day with 2% H_2SO_4, without solution taking place, and the product isolated from this gave no nitrobenzoate, thus showing no alcoholic properties.

Action of aniline on $C_{15}H_{24}O\ CL_2$.

On a water bath were heated together for several hours, a quantity of $C_{15}H_{24}O\ CL_2$ with a slight ~~excess~~ excess of aniline over that required to remave two molecules of H CL from the compound. The excess aniline was neutralised with dilute HCL and the acid solution extracted with ether. On drying and boiling down the ether solution a deep brown viscous oil was obtained, which still contained appreciable quantities of CL and was unsaturated to Br_2 and $KMnO_4$.

Attempt to prepare $C_{15}H_{24}O$ from $C_{15}H_{24}O\ CL_2$.

(1) by Na-amalgam.

A quantity of $C_{15}H_{24}O\ CL_2$ was dissolved in purified alcohol and a little water added (see Weyle Methoden, Spezeiller Teil, 'Reduction of CL---OH groups to H---OH groups) and an excess of Na-amalgam freshly made up added. On standing two days, with occasional shaking, all the Na had gone into solution. The remaining Hg was recovered, retreated with Na to form Na-amalgam and again added to the alcoholic solution

of the oxide. When the Na had all reacted with the alcohol and the Hg removed, the alkaline solution was neutralised with CO_2 and filtered The filtrate was cleared of alcohol by distillation on the waterbath and the residue was a bright yellow oil. This was distilled at 1 mm. pressure when the major part boiled over At 120°-130° C. By a Carius estimation for Cl it was shown to contain 15.6% of that element. This showed incomplete dechlorination, and to find out if the dechlorinated process was proceeding strictly in a way to replace a Cl atom by a H, an ultimate analysis was performed and the following figures were found:-

C = 69.0% : H = 9.05% : CL = 15.6 % : (experimental)

The percentage composition of $C_{15}H_{24}O\,CL_2$ and $C_{15}H_{26}O$ are given here,

For $C_{15}H_{24}O\,CL_2$: C = 61.8% : H = 8.24% : CL = 24.3% :

For $C_{15}H_{26}O$: C = 81.08% : H = 11.7% : CL = Ø 7.22% :

Although a calculation of the oxide and dechlorinated oxide in this product calculated from (1) the carbon content of the three (2) the CL contents (3) the H contents , are not in exact agreement, these figures serve to show that the reaction was a simple replacement of CL_2 by H_2 in the molecule.

The partly dechlorinated was further treated with Na-amalgam for 10 days, the amalgam being renewed as required. It was found best on each renewal of the amalgam to neutralise the alcoholic solution and filter off the Na CO_3 each time, as when the alcoholic solution becomes strongly alkaline the rate of evolution of H_2 from the amalgam becomes

very slow indeed. The oil after this further treatment gave, on a Carius estimation, a value of 14.4% CL, i.e., only a decrease of 1.2% CL from the previous one. The dechlorination was not continued by this method.

(2) By Cu-Zn dust in alcohol.

$C_{15}H_{24}O\ CL_2$ was dissolved in purified alcohol with about 10% water added, and refluxed on a water-baht constantly for about three weeks, with small quantities of Cu-Zn dust, freshly prepared, added during that period. The Cu-Zn dist was prepared by adding fine Zn dust to a solution of $CuSO_4$ in water, shaking thoroughly, and decanting the liquid from the Cu-Zn on settling. The oil recovered after this treatment still contained CL and an attempt to effect a separation of the presumably lower boiling dechlorinated oxide, by fractional distillation at 1mm., failed. The lowest fraction isolated in this procedure boiled at 94°-100° C/1mm. and showed stilla 4.11% CL content by a Carius estimation.

Oxidation of $C_{15}H_{24}O\ CL_2$ by H_2O_2,

$C_{15}H_{24}O\ CL_2$ (one molecular quantity) was dissolved in four times its weight of glacial acetic acid and H_2O_2 (one molecular quantity) added. The flask containing the reacting substances stood three days at room temperature, followed by about two hours on a water bath at 100°C. At a pressure of 10mm. most of the acetic acid was boiled over and collected. This was first

tested for neutral substances by complete neutralisation of the ~~aq~~ acetic acid and extraction of the neutral solution solution by ~~eth~~ ether, but no neutral substances were found.

Neither did the neutral solution when acidified by dil. H_2SO_4 and extracted with~~b~~ ether give any acidic product other than acetic acid which was identified by its boiling point. From the residue remaining after distillation a neutral viscous brown oil was obtained by extraction with ether of the residue made alkaline with conc. ~~NaOH~~ $NaCO_3$ solution. This oil only occurs in small yield and on analysis of a purified specimen, which was found to boil at 140°-155°C/0.7mm, no satisfactory formula could be calculated for the combustion figures found.

When the neutral product was isolated from the alkaline solution, the latter was acidified with dil. H_2SO_4 and evapourated to dryness On extraction with ether a brown oil was recovered by distillation from the dried ether solution, and this oil on standing for a time deposited crystals which on purification from ether were identified as succinic acid by a melting point. Acetone was next used as extracting solvent and by this means a good yield of an acid was~~b~~ obtained on distilling off the acetone. This acid was a dark brown viscous oil which was not further characterised, and is the main product of the oxidation of $C_{15}H_{24}O\ Cl_2$ by H_2O_2.

Molecular weight of $C_{15}H_{24}O\ Cl_2$.

This was determined by noticing the depression of the freezing point of benzene, caused by the oxide when dissolved in that

solvent. W

Wt. of benzene = 54.6200 -33.4286 = 21.1914 gm.

Wt.of oxide = 32.4700 -32.3920 = 0.760 gm.

Readings on the Beckmann for freezing point of benzene,

(1) 2.62 (2) 2.62. (3) 2.625.

Readings for depressed freezing point,

(1) 2.56 (2) 2.56 (3) 2.56.

∴ depression = 0.065 C.

Constant for C_6H_6 = 50,

$$\therefore \quad M = \frac{KW}{dW} = \frac{50 \times 0.76}{0.065 \times 21.1914} = \quad 276 \text{ approx.}$$

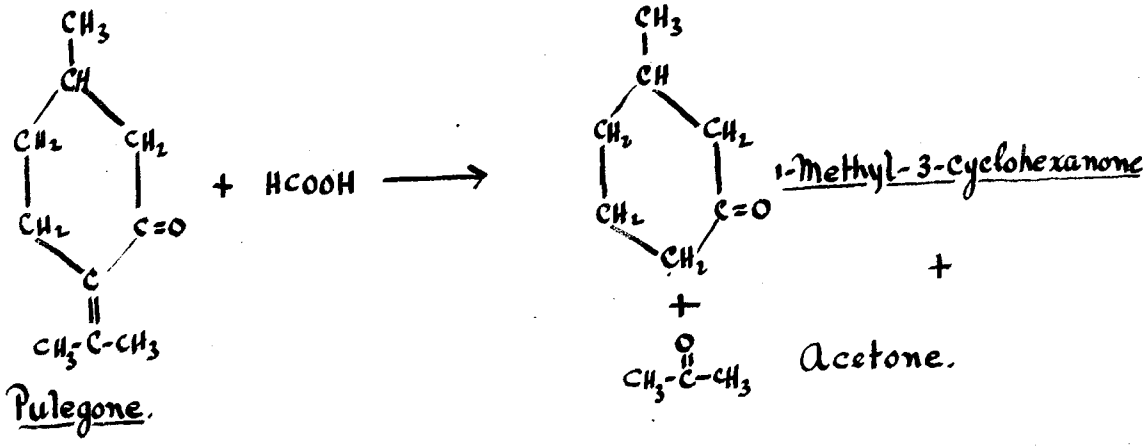
Molecular weight calcularted for $C_{15}H_{14}O\ CL_2$ = 255.5.

PART III.

A NEW PREPARATION OF CARYOPHYLLENE ALCOHOL AND ITS FORMIC ESTER.

A NEW PREPARATION OF CARYOPHYLLENE ALCOHOL AND ITS FORMIC ESTER.

It was found that on refluxing pulegone with anhydrous HCOOH for several days, acetone and methyl-1-cyclohexanone resulted(Wallac Ann.1896.289. 337) as indicated below.



also the action of anhydrous HCOOH on the aliphatic sesquiterpene, citronellene, resulted in theproduction of a cyclo-sesquiterpene(Semmler and Shornitz,Ber 1913.46. 4025)

Inthe hope of either showing the presence of a gem-dimethyl (or isopropylidene grouping), similar to that in pulegone or producing a new tricyclic hydrocarbon(perhaps clovene),equal quantities of dry caryophyllene and anhyd. formic acid were refluxed on the water bath for severarl days. No trace of acetone wasfound,but the oil which was was recovered was fractionated at reduced pressure and the major part passed over 135°-150°C at 10mm.. This fraction consisted of a compound $C_{16}H_{24}O_2$ or $C_{15}H_{24}HCOOH$,and its physical properties were found to be,

B.Pt. 141°-145°C/10mm. $N_d^{20} = 1.4967$. $d^{17} = 1.2$ $[\alpha]_{Hg\ blue.}^{17} = -10.46$.

It was presumably an ester, since it gave no semicarbazone, and this was verified by the fact that on hydrolysis, a crystalline compound was recovered, which when purified melted at 94°-96° C and is identical with caryophyllene alcohol, M.Pt. 94°-96° C described by Wallach and Walker (Ann 271.285-299.)

This is not the ordinary behaviour of anhydrous HCOOH on terpenes, as in many cases ~~in many cases~~ it brings about isomerisation of the hydrocarbon on heating as was seen in the case of citronellene (loc.cit.). Of course the production of terpene esters, e.g. terpineol acetate from pinene, isobornyl acetate from camphene, caryophyllene alcohol from caryophyllene, etc., is well known, but in these cases as ~~glacial~~ glacial acetic acid quantities of 50% H_2SO_4 or 50% $C_6H_5HSO_3$ are added to bring about the addition of the acetic acid molecule (cf Bertram and Walbaum, J.fur Prakt. Chem. 1894.II. 49.1.). The existence of this formic ester also provides a clue to the mechanism of the isomerisations brought about by about by HCOOH in the terpene chemistry, and makes it reasonable to suggest that intermediate esters of formic acid are formed but break down under the conditions of the experimentso that a molecule of HCOOH is eliminated to give a new hydrocarbon.

It is quite possible that the formic ester of caryophyllene is best prepared in this way, for if the usual alcohol-acid esterification were used, dehydration of the alcohol is likely to take place and so diminish the yield of the ester even to the extent of quant-

itative formation of a new hydrocarbon or clovene (cf. Action of P_2O_5 on caryophyllene alcohol,' Wallach and Walker Ann. 271. 285-299.) It is possible also, that sesquiterpenes which by the usual treatment by acetic and sulphuric acids fail to give corresponding alcohols (e.g. cadinene, humulene.) may react with HCOOH to give the alcohol via the formic ester.

Preparation of formic ester of caryophyllene alcohol.

In an attempt to, firstly break off three carbon atoms from the $C_{15}H_{24}$ molecule in the form of acetone, and secondly bring about the closing of another ring in the caryophyllene molecule, 25cc. β-caryophyllene with an equal amount of anhydrous formic acid were heated in a small flask under reflux for several days. Action took place at once, the caryophyllene layer at the top becoming quite red. It was necessary to add some porous pot to prevent violent bumping. When the reaction was complete the reaction mixture was distilled from a water bath, but no distillate came over at that temperature, showing the ~~xxxxx~~ absence of acetone. Having neutralised the excess HCOOH by $NaCO_3$, an extraction with ether of the neutral solution furnished, in the usual way, an oil which was fractionated at 10mm into the following fractions:-

(1) B.P^t. 115°-125° C, N_d^{15} = 1.4083.

(2) B.Pt. 125°-135° C, N_d^{15} = 1.4993.

(3) B.pt. 135°-150° C, N_d^{15} = 1.4989.

Fractions (2) and (3) were again distilled repeatedly till a fraction b.pt. 141°-145° C/10mm. was isolated, weighing about 8 gms or about 35% of original caryophyllene. On analysis of this compound the following

figures were found,

C = 76.9%: H = 10.5%: (experimantal)

and the calculated figures for $C_{15}H_{24}HCOOH$, are

C = 76.8%: H = 10.4%: (calculated).

On treating this compound with semicarbazide acetate in absolute alcohol no crystalline product formed. However on hydrolysis of this oil with 10% alcoholic KOH under reflux condenser on water bath for an hour an oil was isolated after neutralisation by CO_2 and ether extraction, which on standing over night in ice turned crystalline. This new substance is soluble inether, but sparingly so in ligroin and fro a mixture of these a good crystallisation was got. A recrystallised specimen melted at 94°-96° C which is the m.pt. of caryophyllene alcohol.

With a view to increasing the yield of the formic ester, 15 cc of the sesquiterpene were heated at 200°C with 10 cc. anhydrous HCOOH in a sealed tube for about five hours. Having transferred the product to a distillation flask on a sand bath most of the exsess HCOOH was recovered by distillation. The residue was fractionated from a Claisen flask at 10mm. but the required fraction whose purity could only be determined by a tedious method of analysis was found in a yield of about 20% of the starting hydrocarbon.

In conclusion, I wish to tender my thanks to my chief and director, Professor G.G. Henderson, for his helpful supervision of this work, and also for the many personal kindnesses shownto me whilst workimg in his department in the Glasgow Universiey.